

1013.574



PATENT SPECIFICATION

NO DRAWINGS

1013.574

Date of Application and filing Complete Specification: June 8, 1962.

No. 22200/62.

Application made in Czechoslovakia (No. 3564) on June 8, 1961.

Two Applications made in Czechoslovakia (Nos. 1826 1827) on March 24, 1962.

Complete Specification Published: Dec. 15, 1965.

© Crown Copyright 1965.

Index at acceptance:—C2 C(1E5K4, 1E6K4, 1F2A2, 1F2C5, 1F2D3, 1G5A, 1G5B, 1G6B4, 1G6B6, 1H1A3, 1H1B, 1H1C3, 1Q1A, 1Q2, 1Q3, 1Q4, 1Q6C, 1Q8A, 1Q9B, 1Q9C, 1Q9F2, 1Q11D, 1Q11J, 2A3, 2A5, 2A14, 2B3A4, 2B3B, 2B3F, 2B3G1, 2B3G7, 2B3G8, 2R17, 3A13A3A4, 3A13A3B3, 3A13A3F3, 3A14A3C, 3A14A8C, B4A1, B4A2, B4A4, B4C, B4D, B4M)

Int. Cl.:—C 07 d

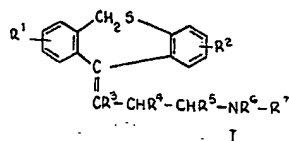
COMPLETE SPECIFICATION

A method for preparing new Derivatives of 6,11-Dihydrodibenz (B,E) Thiepin

We, SPOFA, Sdružení podniků pro zdravotnickou výrobu, a Body Corporate of No. 11a, Husinecká, Prague 3, Czechoslovakia, do hereby declare the invention, for which we pray

5 that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to a method for preparing new 6,11 - dihydrodibenz (b,e) thiepin derivatives of the general formula I



and acid addition salts thereof.

15 In the formula, R¹ and R² (being the same or different, in any position of the aromatic nuclei) each stand for a hydrogen atom, an alkyl-, alkoxy-, aryl-, aralkyl-, or alkylmercapto group, or a halogen atom, and R³, R⁴ and R⁵ either for hydrogen atoms, in which

20 case R⁶ and R⁷ stand for alkyl residues with 1—4 carbon atoms, or, together, an alkylene chain, which may be interrupted with an oxygen atom or a nitrogen atom which may be substituted with an alkyl residue with 1—4

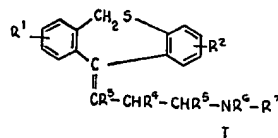
25 carbon atoms, or two of the R³, R⁴ and R⁵ symbols stand for hydrogen atoms, and the third one linked with R⁶ forms an unbranched alkylene chain with 2—4 carbon atoms, in which case R⁷ stands for an alkyl residue with

30 1—4 carbon atoms.

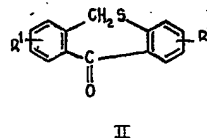
The said new derivatives show a series of significant pharmacodynamical effects, their antidepressive, ataractic, spasmolytic and anti-

histaminic effects being the especially typical ones. They can serve as drugs, especially in some disorders and diseases of the central and vegetative nervous system.

According to the present invention a method of preparing new derivatives of 6,11 - dihydrodibenz (b,e) thiepin having the general formula



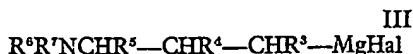
wherein R¹ and R² (being the same or different, in any position of the aromatic nuclei) each stand for a hydrogen atom, an alkyl-, alkoxy-, aryl, aralkyl-, or alkylmercapto group, or a halogen atom, and R³, R⁴, and R⁵ stand either for hydrogen atoms, in which case R⁶ and R⁷ stand for alkyl residues with 1—4 carbon atoms, or, together, an alkylene chain, which may be interrupted with an oxygen atom or a nitrogen atom which may be substituted with an alkyl residue with 1—4 carbon atoms, or two of the R³, R⁴ and R⁵ symbols stand for hydrogen atoms, and the third one linked with R⁶ forms an unbranched alkylene chain with 2—4 carbon atoms, in which case R⁷ stands for an alkyl residue with 1—4 carbon atoms, and acid addition salts thereof, comprises reacting a compound of the general formula II



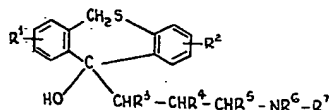
BEST AVAILABLE COPY

AP8

wherein R^1 and R^2 stand for the same as in the formula I, with a Grignard reagent of the general formula III



- 5 wherein R^3 to R^7 stand for the same as in the formula I, and Hal signifies a halogen atom, preferably chlorine, thereupon dehydrating the compound thus obtained, having the general formula IV:



IV

wherein R^1 to R^7 stand for the same as in the formula I, and if desired converting the product obtained to a salt.

- 15 The compounds of the general formula II serving as the starting materials, i.e. the 11-oxo - 6,11 - dihydrodibenz (b,e) thiepins, are available e.g. by cyclisation of suitably substituted S - benzylthio - salicylic acid chlorides or anhydrides in the presence of anhydrous aluminium chloride, by cyclisation of suitably substituted 2 - (phenylmercaptomethyl)-benzoic acids by means of polyphosphoric acid.

- 20 Components for the preparation of the Grignard reagent of the general formula III which can be expediently used are amino alkyl halides, and N-containing heterocyclic halides, such as 3 - dimethylaminopropyl chloride, 3-piperidinopropyl chloride, 3 - morpholinopropyl chloride, 3 - pyrrolidinopropyl chloride, 30 3 - (N - methylpiperazino) - propyl chloride, 2 - (N - methyl - 2 - piperidyl) - ethyl chloride, N - methyl - 3 - piperidylmethyl chloride, and N - methyl - 4 - piperidyl chloride.

- 35 The compounds of the general formula IV obtained according to the Grignard reaction can be easily converted to the desired products of the general formula I by action of various dehydrating agents, for example diluted mineral acids, alcoholic or ethereal HCl-solution, acetyl chloride, thionyl chloride, and iodine. Said compounds I represent viscous oily liquids or crystalline substances. In some instances they exist in the form of cis-trans isomers, which can be separated by fractional crystallisation of their salts.

- 40 Among various salts which can be obtained by neutralising compounds of the general formula I, in the form of free bases, with acids, the hydrochlorides are especially significant, being readily crystallisable and water - soluble, and therefore suitable to be worked up to medicinal preparations.

Embodiments of the invention will now be described by way of example: —

EXAMPLE 1

To a mixture of 1.5 gm. magnesium and 15 ml anhydrous ether are added a few drops of ethyl bromide, and when the reaction has started a solution of 9 ml. 3 - dimethylaminopropyl chloride in 15 ml ether is added. The reaction mixture is heated under reflux to boil gently for 2 hours. Thereupon, while stirring, a solution of 6.5 gm 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin in 25 ml benzene is dropwise introduced. The reaction mixture is stirred for 18 hours and boiled under reflux, and after cooling decomposed by addition of 100 ml 10% by wt. ammonium chloride solution. 100 ml chloroform is added and, after thorough shaking, the organic phase is separated and the aqueous phase again extracted with chloroform. The chloroform extracts are united, dried over potash and evaporated. The residue (9.0 gm) crystallises out on standing. Upon recrystallisation from benzene-petroleum ether mixture the 11 - hydroxy - 11 - (3 - dimethylaminopropyl) - 6,11 - dihydrodibenz (b,e) thiepin thus obtained has melting point at 130—131°C.

8.0 gm of the latter crude carbinol, dissolved in 70 ml 3N H_2SO_4 , is heated for 5 min. to boiling and then treated with charcoal and filtered. The filtrate is made alkaline with a 20% by wt. NaOH solution, the base eliminated is extracted with chloroform, the extract dried over potash and evaporated to dryness. The residue is then distilled in vacuo. There is obtained 4.3 gm 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin, having b.p. 162—164°C. By dissolving in ethanol and neutralising with ethereal HCl-solution the crystalline hydrochloride is obtained, which on re-crystallisation from an ethanol - ether mixture has a m.p. 215—217°C.

EXAMPLE 2

Into a solution of 3 - dimethylaminopropyl magnesium chloride (prepared from 4.5 gm. magnesium and 22.4 gm. 3 - dimethylaminopropyl chloride in 80 ml ether) a solution, prepared from 22.1 gm. 2 - methyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin in 150 ml of thiophene-free benzene, is dropwise introduced during a short period of time. The reaction mixture is stirred for 16 hours in a water-bath kept at 60°C., then cooled down and decomposed by adding dropwise to 200 ml of a 10% by wt. ammonium chloride solution. The benzene - ether layer is separated, the aqueous layer extracted twice with 50 ml benzene each time, the organic liquid extracts united, dried over potash, and the solvents evaporated at reduced pressure. The crystalline residue yields on crystallisation from 120 ml ethanol 18 gm. (60% of theoretical yield) of the desired 2 - methyl - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydrodibenz (b,e) thiepin, having m.p. 142—143°C.

10 gm of the said carbinol, dissolved in 100 ml 3N—H₂SO₄, is heated for 20 minutes to boiling. When cooled the solution is made alkaline with concentrated ammonia, and the base thus eliminated extracted with benzene, the extract dried over potash and evaporated at reduced pressure. The residue is dissolved in 11 ml absolute ethanol, and by addition of ethereal HCl-solution in slight excess, the hydrochloride precipitated. In this way 8.4 gm. (80% of theoretical) of crystalline 2-methyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 218—220°C., is obtained. By repeated recrystallisation from ethanol - ether mixture there are obtained products melting consistently at 220°C. There is evidently the question of which of the two possible geometric isomers is present.

The compound 2 - methyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin, serving as the starting material, can be prepared as follows:—Into polyphosphoric acid (obtained from 157 gm. phosphorus pentoxide and 105 ml of 85% by wt. phosphoric acid) 49 gm. 2 - (p - tolylmercaptomethyl) - benzoic acid is introduced in portions at 140°C. while stirring. The mixture is stirred for further 2 hours at the above quoted temperature, and after partial cooling poured into a large excess of ice-water mixture. The product eliminated is extracted with chloroform, the extract washed with a 10% by wt. NaOH solution, dried over potash and evaporated. The crystalline residue is purified by recrystallisation from ethanol, m.p. 119—121°C. yield 35 gm. (76.2% of theoretical).

EXAMPLE 3

Analogous to Example 2, a Grignard reagent prepared from 8.7 gm 3 - dimethylaminopropyl chloride is made to react with 8.6 gm. of 4 - methyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin. There results in good yield the 4 - methyl - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydrodibenz (b,e) thiepin, having m.p. 164—166°C. (ethanol).

4.3 gm of the said carbinol with 53 ml 3N—H₂SO₄ is heated for 20 min. to boiling. The clear solution obtained is worked up in the same manner as in Example 2. There is obtained 3.9 gm of 4 - methyl - 11 - (3 - dimethyl - aminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 195—197°C. (ethanol-ether).

The starting compound 4 - methyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin is obtained by cyclisation of 2 - (o - tolylmercaptomethyl) benzoic acid at 110°C. by aid of polyphosphoric acid. Yield is 84% of theoretical, m.p. 109—111°C.

EXAMPLE 4

Analogous to Example 2 a Grignard reagent prepared from 16.3 gm 3 - dimethylaminopropyl chloride is made to react with 17

gm 2 - ethyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin. There is obtained in good yield 2 - ethyl - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydrodibenz (b,e) thiepin, having m.p. 138—139°C. (ethanol).

5.5 gm of this carbinol with 150 ml 3N—H₂SO₄ is heated for 20 min. to boiling. The solution obtained is worked up in the same manner as in Example 2. There is obtained 3.3 gm (57% of theoretical) of 2-ethyl-11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 200—201°C.

The starting compound 2 - ethyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin is obtained by cyclisation of 2 - (p - ethylphenylmercaptomethyl) - benzoic acid at 100°C. by aid of polyphosphoric acid. Yield is 74% of theoretical m.p. 52—53°C. (cyclohexane).

EXAMPLE 5

Analogous to Example 2 a Grignard reagent prepared from 18.1 gm 3 - dimethylaminopropyl chloride is made to react with 20 gm. 2 - isopropyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin. There results in 51% of theoretical yield 2 - isopropyl - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydrodibenz (b,e) thiepin, having m.p. 169—170°C. (benzene-petroleum ether).

7.0 gm of this carbinol with 150 ml 3N—H₂SO₄ is heated for 25 min. to boiling. By working up the reaction mixture in the same manner as in Example 2 5.3 gm of the 2 - isopropyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 198—200°C. (ethanol-ether) is obtained.

The starting compound 2 - isopropyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin (m.p. 94—95°C., ethanol) is prepared by cyclisation of the 2 - (p - isopropylphenylmercaptomethyl) - benzoic acid, analogous to preceding Examples.

EXAMPLE 6

Analogously, starting from the 2 - (n-butyl) - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin (with m.p. 58—60°C.) the 2 - (n - butyl) - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydrodibenz (b,e) thiepin (with m.p. 122°C., ethanol) is obtained, from which by dehydration the 2 - (n - butyl) - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 98—101°C./ethanol - ether/ is prepared.

EXAMPLE 7

A Grignard reagent, prepared from 2.4 gm magnesium and 13.4 gm 3 - dimethylaminopropyl chloride in 20 ml anhydrous ether, is made to react with 15.8 gm of 2 - benzyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin dissolved in anhydrous tetrahydrofuran. There is obtained 10 gm of 2 - benzyl - 11 - (3 -

dimethylaminopropyl) - 11 - hydroxy - 6,11-dihydrodibenz (b,e) thiepin (with m.p. 122—123°C., ethanol) which upon processing yields the crystalline and hygroscopic 2 - benzyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride.

The starting compound 2 - benzyl - 11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin (with m.p. 155—156°C., benzene) is prepared by cyclisation of the 2 - (p - benzylphenylmercaptomethyl) - benzoic acid.

EXAMPLE 8

A Grignard reagent, prepared from 10.75 gm magnesium and 53.75 gm 3 - dimethylaminopropyl chloride in 250 ml anhydrous ether, is made to react with 53.0 gm 2-fluoro-11 - oxo - 6,11 - dihydrodibenz (b,e) thiepin dissolved in 200 ml of thiophene - free benzene. By the usual procedure 16.2 gm of 2-fluoro - 11 - (3 - dimethylaminopropyl) - 11 - hydroxy - 6,11 - dihydrodibenz (b,e) thiepin, having m.p. 155—156°C., is obtained.

A mixture consisting of 7.0 g. of the said carbinol, 50 ml chloroform and 6.5 gm acetyl chloride is heated for 5 hours under reflux. It is then evaporated at reduced pressure, and the residue formed by the crude 2 - fluoro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride is purified by recrystallisation from an ethanol-acetone - ether mixture. The yield of the purified product, having m.p. 200—202°C., amounts to 4.2 gm.

This product represents evidently a mixture of the two possible geometric isomers, since in extremely slow crystallisation there can be observed development of two clearly different crystal types, which can be mechanically separated. The one form melts at 229°—231°C., the other one at 190°—194°C.

The compound 2 - fluoro - 11 - oxo - 6,11-dihydrodibenz (b,e) thiepin (m.p. 101—104°C. ethanol) serving as the starting material is prepared by cyclisation of 2 - (p - fluoro - phenyl mercaptomethyl) - benzoic acid.

In analogous manner to the preceding Examples additional compounds of the general formula I can be prepared: —

2 - chloro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 244—247°C. (ethanol). The corresponding ketone II melts at 136°C., and the carbinol IV at 152—153°C. (benzene).

9 - chloro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 184—185°C. (ethanol). The corresponding ketone II melts at 89—90°C. (ethanol), and the carbinol IV at 144—145°C. (ethanol). 2,9 dichloro-11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 233—236°C. (ethanol-ether). The corresponding ketone II melts at 135—136°C.

(ethanol), and the carbinol IV at 166—167°C. (ethanol).

2 - bromo - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 260—261°C. (ethanol). The corresponding ketone II melts at 151—156°C. (acetone-ethanol), and the carbinol IV melts at 164—165°C. (ethanol).

If in the preparation of the Grignard reagent of the general formula III e.g. 3-piperidinopropyl-, 3 - morpholino - propyl-, 3-pyrrolidinopropyl-, 3 - (N¹ - methylpiperazino) - propyl-, 2 - (N - methyl - 2 - piperidyl) - ethyl-, N - methyl - 3 - piperidylmethyl-, or N - methyl - 4 - piperidyl chlorides are used, there are obtained by analogous reactions with the corresponding ketones of the general formula II and the further usual processing, the following compounds of the general formula I: —

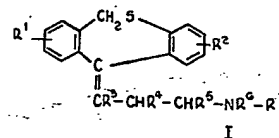
11 - (3 - piperidinopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 260—262°C. (methanol); 11 - (3 - N¹ - methylpiperazinopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 256—263°C. (ethanol-ether);

11 - (2 - N - methyl - 2 - piperidyl-ethylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 198—201°C. (ethanol - ether);

11 - (N - methyl - 3 - piperidylmethylene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 191—194°C. (ethanol-ether); 11 - (N - methyl - 4 - piperidylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 267—272°C. (ethanol-ether).

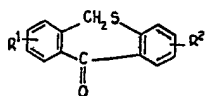
WHAT WE CLAIM IS: —

1. A method of preparing new derivatives of 6,11 - dihydrodibenz (b,e) thiepin having the general formula I



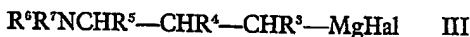
wherein R¹ and R² (being the same or different, in any position of the aromatic nuclei) each stand for a hydrogen atom, an alkyl-, alkoxy-, aryl, aralkyl-, or alkylmercapto group, or a halogen atom, and R³, R⁴, and R⁵ stand either for hydrogen atoms, in which case R⁶ and R⁷ stand for alkyl residues with 1—4 carbon atoms, or, together, an alkylene chain, which may be interrupted with an oxygen atom or a nitrogen atom which may be substituted with an alkyl residue with 1—4 carbon atoms, or two of the R³, R⁴ and R⁵ symbols stand for hydrogen atoms, and the third one linked with R⁶ forms an unbranched alkylene chain with

2—4 carbon atoms, in which case R⁷ stands for an alkyl residue with 1—4 carbon atoms, and acid addition salts thereof, comprising reacting a compound of the general formula II

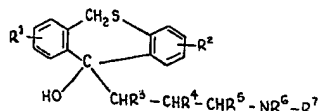


II

wherein R¹ and R² stand for the same as in the formula I, with a Grignard reagent of the general formula III



- wherein R³ to R⁷ stand for the same as in the formula I, and Hal signifies a halogen atom, preferably chlorine, thereupon dehydrating the compound thus obtained having the general formula IV:



IV

wherein R¹ to R⁷ stand for the same as in the formula I, and if desired converting the product obtained to an acid addition salt.

2. 11 - (3 - dimethylaminopropylidene)-6,11 - dihydrodibenz (b,e) thiepin, having the boiling point 162—164°C., and the hydrochloride thereof, having melting point 215—217°C.
3. 2 - methyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 218—220°C.
4. 4 - methyl - 11 - (3 - dimethylaminopropylidene)-6,11 - dihydrodibenz (b,e) thiepin hydrochloride having m.p. 195—197°C.
5. 2 - ethyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 200—201°C.
6. 2 - isopropyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 198—200°C.
7. 2 - n - butyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 98—101°C.
8. 2 - benzyl - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, hygroscopic.
9. 2 - fluoro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 200—202°C.
10. 2 - chloro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 244—247°C.
11. 9 - chloro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 184—185°C.
12. 2,9 - dichloro - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 233—236°C.
13. 2 - bromo - 11 - (3 - dimethylaminopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, having m.p. 260—261°C.
14. 11 - (3 - piperidinopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 260—262°C.
15. 11 - (3 - N¹ - methylpiperazinopropylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 256—263°C.
16. 11 - (2 - N - methyl - 2 - piperidylethylidene) - 6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 198—201°C.
17. 11 - (N - methyl - 3 - piperidylmethylidene)-6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with m.p. 191—194°C.
18. 11 - (N - methyl - 4 - piperidylidene)-6,11 - dihydrodibenz (b,e) thiepin hydrochloride, with mp. 267—272°C.
19. A method of preparing new derivatives of 6,11 - dihydrodibenz (b,e) thiepin as defined in claim 1 according to any of the Examples.
20. Derivatives of 6,11 - dihydrodibenz (b,e) thiepin as defined by formula I obtained by any of the methods of claim 19 or its obvious chemical equivalent.

H. D. FITZPATRICK & CO.,
Chartered Patent Agents,
94 Hope Street, Glasgow, C.2.
and

3 Gray's Inn Square, London, W.C.1.